

## **Comparison of Three Commercial Knowledge Bases for Detection of Drug-Drug Interactions in Clinical Decision Support**

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## **ABSTRACT**

**Objective:** To compare three commercial knowledge bases (KB) used for the detection and avoidance of potential drug-drug interactions (DDI) in clinical practice.

**Methods:** Drugs in the DDI tables from First DataBank (FDB), Micromedex and Multum were mapped to RxNorm. The KBs were compared at the clinical drug, ingredient and DDI rule levels. The KBs were evaluated against a reference list of highly significant DDIs (the “ONC list”). The KBs and the ONC list were applied to a prescription data set to simulate their use in clinical decision support.

**Results:** The KBs contained 1.5 (FDB), 4.5 (Micromedex) and 4.8 (Multum) million clinical drug pairs. Altogether, there are 8.6 million unique pairs, of which 79% were found only in one KB and 5% in all three KBs. However, there was generally more agreement than disagreement in the severity rankings, especially in the contraindicated category. The KBs covered 99.8% - 99.9% of the alerts of the ONC list and would have generated 25 (FDB), 145 (Micromedex) and 84 (Multum) alerts per 1,000 prescriptions.

**Conclusion:** The commercial KBs differ considerably in size and quantity of alerts generated. There is less variability in severity ranking of DDIs than suggested by previous studies. All KBs provide very good coverage of the ONC list. More work is needed to standardize the editorial policies and evidence for inclusion of DDIs to reduce variation among knowledge sources and improve relevance. Some DDIs considered contraindicated in all three KBs may be possible candidates for adding to the ONC list.

## **INTRODUCTION**

Medications remain one of the most common modalities of treatment in modern health care, yet they are also an important iatrogenic cause of morbidity and even mortality. It has been estimated that medication errors account for 7,000 deaths annually in the US, corresponding to 1 per 131 outpatient and 854 inpatient mortalities.<sup>1</sup> Inpatient adverse drug events alone have been estimated to cost a total of \$2 billion per year.<sup>1</sup> Not all adverse events can be avoided, but drug-drug interactions (DDI) may be among the most preventable and manageable because of their potential predictability. A clinically significant DDI is defined as an unintended modification in the effect of a drug when administered with another drug. It can be an increase or a decrease in the action of either drug, or an adverse effect not normally associated with the drugs,<sup>2</sup> and is actionable (i.e., some action should be taken or risk management plan considered). One study reported that DDI accounted for 17% of adverse drug reactions leading to hospitalization.<sup>3</sup> In another study, 4.4% of elderly patients received prescriptions with a risk of severe interactions.<sup>4</sup>

Aging populations, multiple co-morbidities, polypharmacy and frequent launch of new drugs are cited as factors that contribute to the frequency and seriousness of DDIs.<sup>5-7</sup> In the US, 29% of adults are taking five drugs or more.<sup>8</sup> Among those aged 65 years or older, 17 – 19% take at least ten drugs.<sup>8</sup> A recent study confirmed that over five years (2006 – 2011), the risk of major DDIs has nearly doubled in geriatric patients (8.4% to 15.1%).<sup>9</sup> Polypharmacy directly affects the ability of health care professionals to recognize potential DDIs. As the number of co-prescribed drugs increase, the potential pairwise interactions increase exponentially. Weideman et al found that clinician DDI recognition rates decreased significantly as the number of drugs increased. Even among trained pharmacists, none detected all interactions when there were eight

or more drugs.<sup>10</sup> Furthermore, in a multi-provider situation the prescribing clinician may not be familiar with, or even aware of, all the patient's medications. All these factors suggest that clinical information systems that can retrieve all medications a patient is using and have the ability to detect and remind providers about DDIs (by displaying warning messages or interruptive alerts) are becoming more and more necessary for patient safety. Indeed, computerized physician order entry (CPOE) with clinical decision support (CDS) capabilities has been mandated by national programs such as the Meaningful Use of EHR incentive program, and strongly recommended by patient safety advocacy organizations such as the Leapfrog Group.<sup>11, 12</sup>

### **Background and significance**

A comprehensive, accurate and evidence-based knowledge base (KB) is the prerequisite to the effective deployment of a CDS capable of preventing and managing DDIs. Since the resources and expertise needed to develop and implement a home-grown DDI KB are only available to a few large academic centers, most organizations choose to purchase their KBs from commercial vendors.<sup>2</sup> The editorial policies for DDI evidence inclusion and timeliness of the KB updates, as well as unique EHR vendor implementation choices directly affect a system's alerting capabilities and CDS advice that is offered to clinicians. Previous studies have highlighted the variability between various sources of DDI knowledge, whether they are proprietary or in the public domain.<sup>13-23</sup> Vitry found that 14 – 44% of major DDIs listed in one compendium were not listed in other compendia.<sup>13</sup> Hazlet et al tested nine DDI software programs and found that the software programs failed to detect clinically relevant DDIs one third of the time, with sensitivity and specificity ranging from 0.44 – 0.88 and 0.71 – 1.0 respectively.<sup>18</sup> The variability

was explained by both KB content and software implementation differences. In view of the variation, Smithburger et al suggest that more than one knowledge source should be used,<sup>19</sup> and that information in proprietary KBs be reviewed by clinical experts.<sup>24</sup> While these suggestions seem logical, financial constraints and availability of expertise may limit their feasibility.

Currently most health care organizations are still relying on a single proprietary KB.<sup>25</sup>

Inconsistent evaluation and classification of interactions have been cited as some of the factors contributing to excessive DDI alerts.<sup>26</sup> A recent publication describing methodologies for unifying editorial policy decisions and criteria for evidence inclusion of DDI has also been pursued as a solution.<sup>27</sup> DDI alert customization capabilities are necessary because of the uniqueness of patient populations served by systems and local treatment guidelines, and are reported to help improve the provider acceptance rates of interruptive alerts, but will also introduce more variability across institutions.<sup>28</sup>

In this study, we performed a comprehensive comparison of three commercial DDI KBs widely used by hospitals, clinics and pharmacies. First, we did a direct comparison of the KBs' lists of interacting drug pairs and their severity rankings to assess their overlap. Second, we used a reference list of highly significant DDIs to assess whether each KB alone would provide sufficient coverage of these high priority cases.<sup>29</sup> Third, we applied the KBs to a prescription dataset to see whether the differences observed among the KBs will translate into different rates and patterns of DDI alert generation. To our knowledge, such a comprehensive comparison of commercial DDI KBs has not been performed.

## **METHODS**

### **Acquiring DDI information from vendors and mapping to RxNorm**

We contacted five commercial drug knowledge base vendors that provide prescription decision support to clinicians. First Databank (FDB), Micromedex and Multum agreed to participate in our study, while MediSpan and Gold Standard declined. Our study only considered DDIs ranked as contraindicated, major/severe and moderate by the KBs. Minor DDIs and interactions with herbal remedies were excluded, because they were less important and tended to be less consistently represented. We mapped the drugs in the KBs to RxNorm,<sup>30</sup> the U.S. interoperability standard drug terminology. We used two RxNorm clinical drug term types, SCD (semantic clinical drug e.g., Azithromycin 500 MG Oral Tablet) and GPCK (generic drug pack e.g., 6 Pack of Azithromycin 500 MG Oral Tablet) which specified the ingredient(s), dose form, route and strength. FDB and Multum provided their own RxNorm mapping tables. For Micromedex, we mapped first to RxNorm ingredients by lexical matching supplemented by manual review, and then navigated to all corresponding SCD and GPCKs, restricted to the dose form and route specified in Micromedex. We used the latest version of RxNorm when we acquired the KBs (May 2014).

### **Comparing interactions across KBs**

A master table was created for each KB, with all DDIs represented as pairs of RxCUIs (RxNorm concept unique identifiers) together with their severity ranking. Each pair of drugs was listed only once, i.e., (A, B) and (B, A) were considered equivalent. If a pair of drugs was assigned more than one severity ranking in a KB (e.g., multi-ingredient formulation with several

interactants), we only kept the highest-ranking entry. We assessed the overlap across KBs by matching the RxCUI pairs.

We also assessed overlap at the ingredient and drug interaction rule (“DDI rule”) levels. Clinical drugs were rolled up to their ingredients using the relationships in RxNorm. Multi-ingredient drugs were excluded in this analysis because it was not possible to pinpoint the interacting ingredient, and the ingredient-level interaction would be captured by the single ingredient formulations anyway. In the KBs, DDIs were grouped under DDI rules to facilitate content management and display of alert messages. Each DDI rule was associated with a textual description (known as a monograph). For example, there was a monograph for all DDIs between tricyclic antidepressants and sympathomimetics. We rolled up clinical drug pairs to their corresponding rules, excluding those that were grouped under multiple rules (e.g., multi-ingredient drugs). We considered DDI rules from two KBs to be overlapping if they shared at least one clinical drug pair.

### **Comparing interactions from KBs against a reference source**

In order to address the challenges of alert burden and its impact on EHR adoption, the Office of the National Coordinator for Health Information Technology (ONC) commissioned a consensus-based effort to identify a subset of highly significant DDIs, for which interruptive warnings should be generated in all EHRs.<sup>29</sup> The ONC high-priority list (“ONC list”) was developed from candidate interactions identified by Partners Healthcare that were then vetted by a stakeholder panel including medication knowledge base vendors, EHR vendors, clinical experts and representatives from federal or private agencies involved in the regulation of medication use. The

panel attained consensus on 15 DDI rules at three levels of specification: drug class-drug class, ingredient-drug class and ingredient-ingredient. The ONC list enumerated class members for all drug classes except QT prolonging drugs and tricyclic antidepressants. We expanded all the ONC DDI rules to the ingredient level. For QT prolonging drugs, we used the web resource CredibleMeds as recommended, limited to drugs associated with the highest risk of torsades de pointes (known as List 1).<sup>31</sup> For tricyclic antidepressants, class members were determined by consulting pharmacology textbooks. To align with the KB master tables, we mapped the ONC list first to RxNorm ingredients, then propagated to SCD/GPCKs, restricting to systemic dose forms (e.g., oral tablets, injections).

We analyzed the coverage of the ONC list by the KBs at the ingredient level. We considered that an ONC ingredient-level DDI was covered if at least one of the clinical drug pairs for that DDI was found in a KB. Since the ONC list was supposed to be highly significant and recommended to be used in all EHRs, any ONC DDI missing from a KB was reviewed by a KB expert to ascertain the reason for absence. Conversely, we selectively reviewed DDIs that were ranked as contraindicated in all three KBs, but not in the ONC list, as they could potentially reflect important DDIs missing from the ONC list.

### **Generating potential DDI alerts from actual prescription data**

We used a dataset from Symphony Health Solutions with one year of prescription-filling data (from July 1, 2011 to June 30, 2012) for patients from Washington DC, Maryland, Virginia and West Virginia. The drugs in the dataset were mapped to RxNorm SCD and GPCK through the NDC codes included in the source data, supplemented by string matching and manual review.



Drugs that were not administered systemically (e.g., topical ointments) were excluded because they seldom caused significant interactions. The period that a patient was exposed to a drug was estimated based on the fill date and days of supply. Two drugs, which might not be prescribed at the same time, were considered to be co-administered if their period of exposure overlapped. The co-administered drug pairs were checked against the three KB and ONC tables to see if DDI alerts would have been generated. We reported the alert rates as a proportion of the total prescriptions. We estimated the number of prescriptions by assuming that the drugs with the same fill date and physician ID belonged to the same prescription.

## **RESULTS**

### **Comparing interactions across KBs**

The number of unique clinical drugs (at the SCD/GPCK level) involved in any DDI ranged from 7,427 to 13,133, among which 5,754 drugs were common to all three KBs (table 1). The size of the KBs varied considerably in terms of drug pairs. FDB had the least drug pairs (1.6 million), followed by Micromedex (4.5 million) and Multum (4.8 million). In all KBs, contraindicated was the smallest category and moderate the largest. Overall, the number of drug pairs that were commonly configured to generate interruptive alerts (contraindicated and major/severe categories together) was 490,260 (30.8%), 2,311,324 (51.9%) and 468,822 (9.8%) for FDB, Micromedex and Multum respectively. Altogether, the three KBs contained 8.6 million unique drug pairs, of which 6.8 million (79.4%) were unique to one KB, 1.3 million (15.5%) were found in two KBs and 0.4 million (5%) in all three KBs (figure 1). The percentage of unique drug pairs (i.e., not found in any other KB) was 35.6%, 65% and 70.9% for FDB, Micromedex and Multum respectively.

		FDB	Micromedex	Multum
Unique drugs		10,279	13,133	7,427
Drug pairs x 1,000 (% of total)	contraindicated	101 (6.3%)	192 (4.3%)	100 (2.1%)
	major/severe	390 (24.5%)	2,120 (47.6%)	368 (7.7%)
	moderate	1,102 (69.2%)	2,139 (48.1%)	4302 (90.2%)
	total	1,592 (100%)	4,450 (100%)	4,771 (100%)

Table 1. Composition of the three knowledge bases

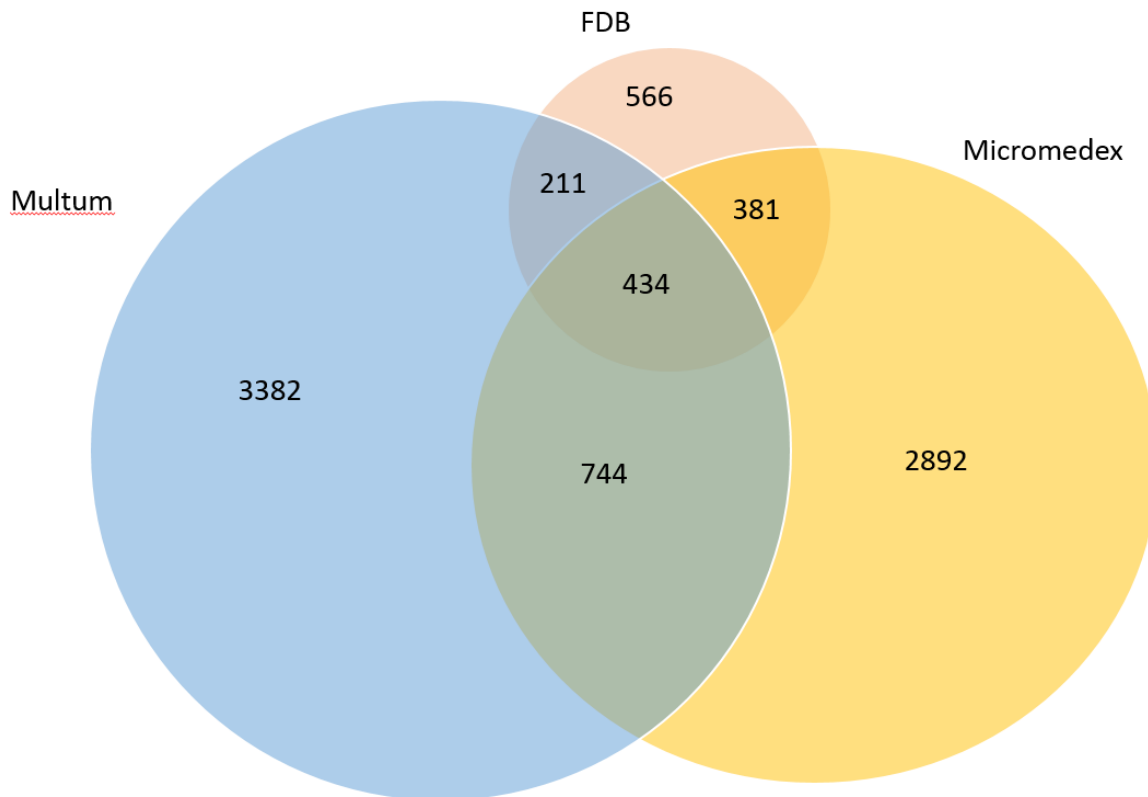


Figure 1. Overlap of clinical drug pairs (numbers in 1,000) between the knowledge bases

KB1 \ KB2			FDB				Micromedex				Multum			
		Total (KB1)	Sev1	Sev2	Sev3	not found	Sev1	Sev2	Sev3	not found	Sev1	Sev2	Sev3	not found
FDB	Sev1	101 (100%)					49 (48%)	20 (20%)	4 (4%)	28 (28%)	35 (34%)	11 (11%)	6 (6%)	49 (48%)
	Sev2	390 (100%)					22 (6%)	129 (33%)	92 (24%)	147 (38%)	19 (5%)	73 (19%)	78 (20%)	219 (56%)
	Sev3	1102 (100%)					3 (0.2%)	201 (18%)	297 (27%)	602 (55%)	2 (0.2%)	90 (8%)	331 (30%)	680 (62%)
Micromedex	Sev1	191 (100%)	49 (25%)	22 (11%)	3 (1%)	119 (62%)					49 (25%)	4 (2%)	10 (5%)	129 (67%)
	Sev2	2119 (100%)	20 (1%)	129 (6%)	201 (9%)	1770 (84%)					8 (0.4%)	176 (8%)	454 (21%)	1481 (70%)
	Sev3	2139 (100%)	4 (0.2%)	92 (4%)	297 (14%)	1747 (82%)					0.9 (0.0%)	30 (1%)	446 (21%)	1663 (78%)
Multum	Sev1	100 (100%)	35 (34%)	19 (19%)	2 (2%)	45 (45%)	49 (48%)	8 (8%)	0.9 (0.9%)	43 (42%)				
	Sev2	368 (100%)	11 (3%)	73 (20%)	90 (24%)	195 (53%)	4 (1%)	176 (48%)	30 (8%)	159 (43%)				
	Sev3	4302 (100%)	6 (0.1%)	78 (2%)	331 (8%)	3887 (90%)	10 (0.2%)	454 (11%)	446 (10%)	3392 (79%)				

Table 2. Pairwise comparison showing number of overlapping clinical drug pairs (numbers in thousands)

between KBs. Each pairwise comparison is outlined by thick borders. The percentages are based on row totals (KB1). The highest percentage (excluding 'not found') in each severity category is highlighted in bold type. Shaded boxes are those in which the severity rankings in two KBs agree (sev1=contraindicated, sev2=major/severe, sev3=moderate)

In table 2, the pairwise comparisons are shown as six grids of 3 x 4 boxes. The number in each box is the number of common drug pairs, and the percentage is based on the total in KB1. For example, comparing FDB to Micromedex (top-middle grid), there are 48,673 shared contraindicated (sev1) DDI drug pairs, corresponding to 48% of all contraindicated DDIs (N=100,697) in FDB. For better visualization, the boxes in which the severity rankings are the same for both KBs are shaded. The highest percentage of shared drug pairs within a severity category (ignoring those not found) is highlighted in bold type. So if the highlighted percentage falls within a shaded box, the severity rankings of the two KBs agree more often than disagree for that severity category. For example, between FDB and Micromedex (top-middle and middle-left grids), the rankings generally agree in most severity categories (5 out of 6 highlighted numbers are in shaded boxes), except that more major DDIs in Micromedex are classified as moderate (9%) in FDB than major (6%) or contraindicated (1%). Overall, 13 out of 18 highlighted percentages are in a shaded box, which is true for all contraindicated categories. Among the shared drug pairs between two KBs, 58% (FDB and Micromedex), 68% (FDB and Multum) and 57% (Micromedex and Multum) have the same severity rankings.

Detailed pairwise comparisons at the ingredient and DDI rule levels can be found in Appendix A (on-line supplementary tables 1 and 2). Generally, the pattern of overlap at the ingredient level is similar to the clinical drug level. At the rule level, the degree of overlap and the agreement in severity ranking are considerably higher, with all but one of the 18 highlighted percentages in shaded boxes. Overall, 48.5% of DDI rules are shared by all 3 KBs, much higher than the ingredient (8.7%) and clinical drug (5%) levels (supplementary table 3).

**Comparing interactions from KBs against a reference source**

		FDB (%)	Micromedex (%)	Multum (%)
Found in KB	contraindicated	591 (57.5%)	496 (48.3%)	491 (47.8%)
	major/severe	189 (18.4%)	398 (38.8%)	324 (31.5%)
	moderate	141 (13.7%)	11 (1.1%)	107 (10.4%)
	not found	106 (10.3%)	122 (11.9%)	105 (10.2%)
Not found in KB because:	versioning	38	92	20
	not on market	33	18	70
	editorial exclusion	13	12	1
	mapping problem	15	0	10
	combination therapy	5	0	4
	other	2	0	0
Total ONC ingredient pairs		1027 (100%)	1027 (100%)	1027 (100%)

Table 3. Coverage of the ONC list ingredient pairs by the KBs

The 15 DDI rules in the ONC list expanded to 1,027 pairs of ingredients. Overall, FDB, Micromedex and Multum did not cover 10.3%, 11.9% and 10.2% of the ONC ingredient pairs respectively (table 3). Versioning (i.e., when the missing DDI was available in a newer version of the KB) accounted for many of the omissions. This shows that the KBs are updated quite frequently as new drug interaction information becomes available. Some drugs in the ONC list (e.g., astemizole, terfenadine) were no longer available on the US market and were not in the KBs. The ONC list included *every* pair of QT prolonging agents considered high risk for causing torsades de pointes. By editorial policy, some KBs only included QT prolonger pairs corroborated by specific evidence (e.g., specific warning in the drug label, clinical reports). Some KBs disagreed with the ONC list of CYP-450 inhibitors. For example, cimetidine and diltiazem were considered as strong CYP3A4 inhibitors in the ONC list, but only moderate inhibitors by two KBs. Some drugs were missed by RxNorm mapping. Some antiretroviral agents were only given as combinations (e.g., tipranavir and ritonavir). For such cases, some

KBs flagged DDI for only one component to avoid duplicate alerts. Some drug pairs were flagged as a different category of alert (e.g., erythromycin and azithromycin were considered as duplicate therapy) and not as DDI. Overall, if we adjust for the unintentional differences (versioning, not on market, mapping, combination therapy and different category), the coverage of the ONC list will become 98.7%, 98.83% and 99.9% for FDB, Micromedex and Multum respectively.

### **Generating potential DDI alerts from actual prescription data**

Our prescription dataset covered 1.9 million patients with 14 million prescriptions and 19 million drug items. Considering all severity levels, the alerts generated by FDB, Micromedex and Multum would be 163, 329 and 751 alerts per 1,000 prescriptions respectively. Counting only contraindicated and major/severe DDIs (usually triggering interruptive alerts), 25, 145 and 84 alerts per 1,000 prescriptions would be generated by FDB, Micromedex and Multum respectively (supplementary table 4).

Applying the ONC list to the prescription dataset would generate 43,047 alerts (3 alerts per 1,000 prescriptions). The overwhelming majority (97.6%) was generated by two DDI rules: statins with protease inhibitors and two QT prolonging drugs (table 4). The remaining 13 ONC rules together accounted for only 2.4% of alerts. Overall, FDB, Micromedex and Multum covered 97.9%, 85.9% and 99.8% of the ONC list alerts respectively. Adjusting for the unintentional differences (versioning, mapping issues etc.), the overall coverage of ONC alerts became 99.8%, 99.9% and 99.9% for FDB, Micromedex and Multum respectively. In FDB, most of the DDIs involving two

QT prolongers were considered moderate, while they were generally ranked higher in the other two KBs.

	ONC alerts (% of total alerts)	% of ONC alerts covered by KB					
		FDB		Micromedex		Multum	
		sev1 and sev2	All severities	sev1 and sev2	All severities	sev1 and sev2	All severities
Lovastatin & Simvastatin with CYP3A4 inhibitors	25,646 (59.6%)	71.9% **	100%	100%	100%	100%	100%
QT prolonging agents with QT prolonging agents	16,362 (38%)	11.5%	95.1%	63.4%	63.5%	93.5%	100%
ALL other ONC DDI rules	1,039 (2.4%)	90.8%	90.8%	89.4%	90.8%	88.1%	92.9%
total	43,047 (100%)	49.4%	97.9%	85.9%	85.9%	97.2%	99.8%

Table 4. DDI alerts generated by the ONC list and their coverage by the KBs (sev1: contraindicated, sev2: major/severe)

\*\*In FDB, interactions between lovastatin/simvastatin with amiodarone, diltiazem, and verapamil are strength-specific, some strengths are contraindicated with these CYP3A4 inhibitors and some interact at a lower severity level

There were 28,410 clinical drug pairs considered contraindicated in all 3 KBs, corresponding to 1,213 ingredient pairs of which 865 pairs (71%) were not in the ONC list. Among them, 160 pairs were actually co-prescribed in our dataset (9 pairs co-prescribed over 100 times). Had the 160 ingredient pairs been included in the ONC list, the total number of ONC alerts would increase by 7,633 (17.7%). Some examples of these interacting ingredient pairs are (frequency of co-prescription in parenthesis):

- Gemfibrozil and Simvastatin (2,561)
- Duloxetine and Rasagiline (223)
- Cyclosporine and Simvastatin (163)
- Chlorpromazine and Ziprasidone (110)
- Nitroglycerin and Sildenafil (83)
- Azithromycin and Dronedarone (64)
- Nitroglycerin and Tadalafil (56)
- Alprazolam and Ketoconazole (53)
- Bupropion and Rasagiline (51)
- Bromocriptine and Sumatriptan (50)

## DISCUSSION

### **Differences among the KBs**

The three commercial DDI KBs differ significantly in their number of clinical drug pairs, and have limited overlap. About two-thirds of the clinical drug pairs in FDB can be found in the other two KBs. The converse is true for Micromedex and Multum, with two-thirds of the drug



pairs being unique to the KB. Contrary to earlier studies, however, we find that there is generally more agreement than disagreement on severity ranking, especially for the most severe interactions. Not surprisingly, the degree of overlap and agreement in severity ranking are considerably higher at the DDI rule level.

### **Impact on clinical decision support**

While it is interesting to compare the KB tables, it is more important to see what the differences mean when they are actually applied in a clinical context. After all, if the differences only involve rarely-prescribed drugs, the impact would be small. We find that the number of drug pairs in a KB only has a weak correlation with the number of alerts generated. Both Multum and Micromedex are three times bigger than FDB, but Multum generates five times and Micromedex two times more alerts. Notably, the amount of alerts in the contraindicated category is disproportionately small for all KBs. Contraindicated DDIs constitute 6.3%, 4.3% and 2.1% of drug pairs in FDB, Micromedex and Multum respectively, but only account for 3.2%, 1% and 0.5% of the alerts. One possible explanation is that drugs with the most severe interactions are actively avoided by prescribers. It is also possible that the prescribers are already using some DDI alerting software that avert contraindicated drug combinations.

All KBs cover over 99% of the alerts generated by the ONC list, which is supposed to be used in all EHRs. However, if the KBs are customized to alert only at the contraindicated and major/severe levels, 2.8 – 50.6% of the ONC alerts will not be fired. Users of the KBs need to consider these cases carefully to see if suppression of these alerts is appropriate, otherwise some important DDIs could be missed.

### **Discrepancies due to QT prolonging drugs and CYP-450 metabolism**

After adjusting for unintentional differences, there is very high coverage of the ONC list ingredient pairs by all 3 KBs (98 – 99.9%). The discrepancies that can be attributed to editorial policies are related to two classes of drugs: QT prolongers and CYP-450 inhibitors. The ONC list includes *all* combinations of a list of QT prolonging drugs with high risk for torsades de pointes (TdP). This represents the single largest source of the ONC ingredient pairs (61%), and 38% of alerts generated. It seems that this “broad-brush” approach of using the CredibleMeds List 1 to determine DDI risk has not been substantiated with evidence. The CredibleMeds website also states that “Because these actions [QT prolongation or TdP] are highly dependent on the circumstances of each drug’s use AND each patient’s clinical characteristics, we do not attempt to rank-order the drugs within each category. Therefore, we do not recommend that these lists be used to rank-order the drugs for their relative toxicity”.<sup>31</sup> The KB editors usually look for additional evidence before alerting against a specific combination of QT prolonging drugs. Different QT prolonger combinations may be assigned different severity levels in a KB, depending on the supporting evidence. Among the 630 QT prolonger combinations in the ONC list, 33 – 44% are considered contraindicated, 25 – 50% major/severe, and 0.3 – 22% moderate by the KBs.

In the ONC list, CYP3A4 inhibitors are involved in four rules, 177 (17%) ingredient pairs and 60% of alerts, while CYP1A2 inhibitors are involved in two rules, 11 (1%) ingredient pairs and 1% of alerts. While the ONC list cites the FDA published list<sup>32</sup> and the Flockhart’s table from the University of Indiana<sup>33</sup> as authoritative sources for CYP-450 inhibitors, the enumerated lists

of CYP3A4 and CYP1A2 strong inhibitors include agents not ranked as strong by these sources. Some KBs also use other reference sources<sup>34</sup> to determine the classification of CYP-450 inhibition, which can lead to different recommendations. Overall, CYP-450 inhibitor class membership causes 14 ingredient pairs to be excluded from at least one KB.

Refinement in identifying significant QT prolonger combinations and better agreement on the classification of CYP-450 inhibitors will improve the concordance between various DDI knowledge sources. The potential clinical impact of these discrepancies is big, as over 98% of alerts generated by the ONC list involve these two drug classes.

### **Completeness of the reference list and other limitations of our study**

Since the ONC list was developed based on the knowledge source of a single health care institute and designed to be a minimum starter set of alerts, one would be justified to question its completeness as a reference list. We did find 865 ingredient pairs that were classified as contraindicated in all KBs but not in the ONC list, some of them were also in our prescription dataset. We reviewed a small sample and confirmed that some should be considered for addition to the ONC list. In addition, we recognize the following limitations. Our study is based on the three commercial DDI KBs that agreed to participate. The KBs were obtained at the beginning of the study and subsequent updates were not considered. Mapping to RxNorm may be incomplete. The extent of unintentional differences (e.g., those caused by versioning and mapping) was assessed in the context of missing ONC DDIs from the KBs, but not for the entire KBs. The prescription dataset we used was a regional dataset over a limited period, and the results may not be generalizable.

## **The way forward**

In view of the variability among different sources of DDI knowledge, it has been suggested that an expert panel with a centralized organizer or convener should be established to develop and maintain a standard set of DDIs for CDS in the United States,<sup>35</sup> as has been done elsewhere.<sup>36</sup>

The intensive logistics and trend towards DDI customization at individual institutions makes this effort difficult to implement. The Pharmacy Quality Alliance (PQA) is convening Stakeholder Advisory Panels for the purpose of creating and maintaining a consensus-based minimum DDI data set.<sup>37</sup> PQA develops medication-use measures in areas such as medication safety, medication adherence and appropriateness. Future DDI knowledge bases though will most greatly benefit not from bigger or better consensus panels but from large scale patient outcomes studies (e.g., derived from EHR) and population data. Improving the availability of DDI evidence in order to best capture high priority drug pairs (or drug triplets), categorize by severity, or assign risk based on pharmacogenomics or phenotype context or other risk factors (e.g., renal impairment) will be the future of not only DDI knowledge base data curation, but other medication-related CDS as well.

## **CONCLUSION**

The three commercial DDI KBs differ considerably in their gross size, and therefore have limited overlap. However, there was generally more agreement than disagreement in the severity rankings, especially in the contraindicated category. Coverage of the ONC high priority list is very high for all three KBs, both in the number of interacting ingredient pairs and potential alerts generated. Disagreements involving QT prolonging drugs and CYP-450 inhibitors account for

most of the omission of ONC DDIs from the KBs. There is evidence to suggest that the ONC list may not cover all highly clinically significant interactions.

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### **Competing Interests Statement**

Joan Kapusnik-Uner is an employee of First Databank, Jean Cunningham is an employee of Truven Health Analytics and Stefanie Higby-Baker is an employee of Cerner Multum.

### **Contributorship Statement**

KWF and OB conceived and designed the study. JKU, JC and SHB provided the source KB tables and documentation, helped with the mapping to RxNorm and validated the results. KWF performed the data analysis. KWF drafted the manuscript and all authors contributed substantially to its revision.

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## APPENDIX A – Supplementary tables

KB1 \ KB2			FDB				Micromedex				Multum			
		Total (KB1)	Sev1	Sev2	Sev3	not found	Sev1	Sev2	Sev3	not found	Sev1	Sev2	Sev3	not found
FDB	Sev1	5226 (100%)					1620 <b>(31%)</b>	1197 (23%)	257 (5%)	2152 (41%)	1844 <b>(35%)</b>	694 (13%)	388 (7%)	2300 (44%)
	Sev2	8025 (100%)					474 (6%)	2430 <b>(30%)</b>	1333 (17%)	3788 (47%)	698 (9%)	1906 (24%)	2566 <b>(32%)</b>	2855 (36%)
	Sev3	15462 (100%)					97 (0.6%)	3167 (20%)	3610 <b>(23%)</b>	8588 (56%)	99 (0.6%)	2302 (15%)	7011 <b>(45%)</b>	6050 (39%)
Micromedex	Sev1	3030 (100%)	1620 <b>(53%)</b>	474 (16%)	97 (3%)	839 (28%)					1751 <b>(58%)</b>	174 (6%)	236 (8%)	869 (29%)
	Sev2	16748 (100%)	1197 (7%)	2430 (15%)	3167 <b>(19%)</b>	9954 (59%)					473 (3%)	3762 (22%)	5821 <b>(35%)</b>	6692 (40%)
	Sev3	18292 (100%)	257 (1%)	1333 (7%)	3610 <b>(20%)</b>	13092 (72%)					60 (0.3%)	743 (4%)	7760 <b>(42%)</b>	9729 (53%)
Multum	Sev1	3689 (100%)	1844 <b>(50%)</b>	698 (19%)	99 (3%)	1048 (28%)	1751 <b>(47%)</b>	473 (13%)	60 (2%)	1405 (38%)				
	Sev2	11924 (100%)	694 (6%)	1906 (16%)	2302 <b>(19%)</b>	7022 (59%)	174 (1%)	3762 <b>(32%)</b>	743 (6%)	7245 (61%)				
	Sev3	86164 (100%)	388 (0.5%)	2566 (3%)	7011 <b>(8%)</b>	76199 (88%)	236 (0.3%)	5821 (7%)	7760 <b>(9%)</b>	72347 (84%)				

Supplementary Table 1. Pairwise comparison showing number of common ingredient pairs between two KBs. The percentages are based on row totals (KB1). The highest percentage (excluding 'not found') in each severity category is highlighted in bold type. Shaded boxes are those in which the severity rankings in two KBs agree (sev1=contraindicated, sev2=major/severe, sev3=moderate).



KB1 \ KB2			FDB				Micromedex				Multum			
		Total (KB1)	Sev1	Sev2	Sev3	not found	Sev1	Sev2	Sev3	not found	Sev1	Sev2	Sev3	not found
FDB	Sev1	362 (100%)					207 (57%)	92 (25%)	19 (5%)	44 (12%)	194 (54%)	72 (20%)	50 (14%)	46 (13%)
	Sev2	484 (100%)					70 (14%)	262 (54%)	89 (18%)	63 (13%)	60 (12%)	188 (39%)	184 (38%)	52 (11%)
	Sev3	691 (100%)					47 (7%)	285 (41%)	290 (42%)	69 (10%)	41 (6%)	147 (21%)	435 (63%)	68 (10%)
Micromedex	Sev1	1724 (100%)	974 (57%)	333 (19%)	88 (5%)	329 (19%)					1140 (66%)	122 (7%)	138 (8%)	324 (19%)
	Sev2	6294 (100%)	476 (8%)	1616 (26%)	1558 (25%)	2644 (42%)					209 (3%)	2243 (36%)	2426 (39%)	1416 (23%)
	Sev3	5020 (100%)	146 (3%)	634 (13%)	1128 (22%)	3112 (62%)					41 (0.8%)	426 (8%)	2945 (59%)	1608 (32%)
Multum	Sev1	230 (100%)	176 (77%)	22 (10%)	4 (2%)	28 (12%)	176 (76%)	21 (9%)	9 (4%)	24 (10%)				
	Sev2	545 (100%)	123 (23%)	216 (40%)	89 (16%)	117 (21%)	57 (10%)	326 (60%)	76 (14%)	86 (16%)				
	Sev3	2459 (100%)	133 (5%)	406 (17%)	637 (26%)	1283 (52%)	87 (3%)	702 (29%)	928 (38%)	742 (30%)				

Supplementary Table 2. Pairwise comparison showing number of overlapping DDI rules between the KBs. Rules from two KBs are considered to overlap if they contain the same pair of drugs. Percentages are based on row totals (KB1). The highest percentage (excluding 'not found') in each severity category is highlighted in bold type. Shaded boxes are those in which the severity rankings in two KBs agree (sev1=contraindicated, sev2=major/severe, sev3=moderate).

	Drug pair level	Ingredient pair level	Rule level
Union of all 3 KBs (%)	8,609,768 (100%)	127,156 (100%)	17,809 (100%)
Present in 1 KB only (%)	6,839,838 (79.4%)	96,821 (76.1%)	3,150 (17.7%)
Shared by exactly 2 KBs (%)	1,336,201 (15.5%)	19,266 (15.2%)	6,019 (33.8%)
Shared by all 3 KBs (%)	433,729 (5%)	11,069 (8.7%)	8,640 (48.5%)

Supplementary Table 3. Overlap between KBs at the clinical drug, ingredient and rule levels across all severities.

		FDB	Micromedex	Multum
DDI alerts per 1,000 prescriptions	contraindicated	5	3	4
	major/severe	20	142	80
	moderate	138	184	667
	total	163	329	751

Supplementary Table 4. DDI alerts generated by applying the 3 KBs to the prescription dataset